



Case Report

A case of paroxysmal pheochromocytoma concurrent with coronary artery aneurysm presenting as acute coronary syndrome

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ABSTRACT

A 51-year-old man recently diagnosed with preclinical Cushing's syndrome complained of chest oppression concomitant with back pain. Following contrast-enhanced computed tomography (CT) to rule out acute aortic dissection, he developed chest symptoms accompanied by elevation of blood pressure to 240/120 mmHg and ischemic electrocardiographic change. Urgent coronary angiography revealed a coronary artery aneurysm (15 mm × 6 mm) in the distal portion of the left anterior descending artery concomitant with coronary flow delay. Re-analysis of the blood sample taken at admission showed elevated plasma catecholamine concentrations, leading to a diagnosis of paroxysmal pheochromocytoma. An adrenal tumor was excised laparoscopically and histologically shown to be a pheochromocytoma. These findings show that coronary artery aneurysm may be a rare complication of pheochromocytoma, and indicate that monitoring of blood pressure or analysis of stored blood samples, if necessary, is essential to detect pheochromocytoma when using contrast medium or glucagon in patients known to have an adrenal incidentaloma. It should be noted that pre-treatment with an α -blocker is necessary when patients who are likely to have pheochromocytoma need to undergo contrast-enhanced CT.

<Learning objective: Coronary artery aneurysm may be a rare complication of pheochromocytoma. Monitoring of blood pressure or analysis of stored blood samples, if necessary, is essential to detect pheochromocytoma when using contrast medium or glucagon in patients known to have an adrenal incidentaloma. It should be noted that pre-treatment with an α -blocker is necessary when patients who are likely to have pheochromocytoma need to undergo contrast-enhanced CT.>

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Introduction

Pheochromocytomas are relatively rare, generally benign tumors, usually located in the adrenal medulla, and related to catecholamine-producing paragangliomas. Typical presentations include headaches, palpitations, sweating, pallor, and sustained or paroxysmal hypertension due to excess catecholamine secretion. Clinical expression of pheochromocytoma can include several acute cardiovascular manifestations, such as hypertensive crisis, shock, acute coronary syndrome, acute heart failure, Tako-tsubo cardiomyopathy, lethal arrhythmia, cerebrovascular events, and aortic dissection [1].

Coronary artery aneurysms are often encountered in clinical cardiology and are usually associated with atherosclerosis, or with inflammatory, infectious, or iatrogenic disease, and are usually located in the proximal coronary artery. The incidence of coronary artery aneurysm has been reported to be 1.4% in autopsy cases and 4.9% in patients with suspected coronary artery disease who undergo coronary angiography [2].

We describe a patient with paroxysmal pheochromocytoma concurrent with coronary artery aneurysm that presented as acute coronary syndrome.

Case report

A 51-year-old man was recently diagnosed with preclinical Cushing's syndrome because of (a) the presence of a right adrenal tumor, an incidentaloma, (b) the lack of overt signs of Cushing's syndrome, and (c) autonomic cortisol secretion as confirmed by

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low-dose (1 mg) and high-dose (8 mg) dexamethasone suppression tests. At that time, however, he showed no definite findings suggestive of another hypothalamo-pituitary adrenal disorder, including pheochromocytoma. He had experienced paroxysmal nocturnal palpitations over the past 5 years. Although he was slightly obese (height, 162.5 cm; body weight, 70.1 kg; body mass index, 26.5 kg/m²), annual routine medical check-ups did not confirm a diagnosis of arrhythmia, hypertension, diabetes, or dyslipidemia. In addition, he had no history of ischemic heart disease, Kawasaki disease, syphilis, or systemic vasculitis.

Five months after the initial endocrinological examinations, the patient presented at the Emergency Service department of our hospital complaining of chest oppression concomitant with back pain, palpitations, non-bilious vomiting, and periodic sweating lasting for 6 h. At the time of arrival, however, his symptoms were somewhat alleviated. A thorough physical examination showed a trace of heavy sweating, despite his being afebrile. He had a regular pulse rate of 82 beats per minute, dual heart sounds with no cardiac murmur, clear lung fields, and no notable findings in the abdomen. Alternatively measured blood pressure showed slight elevation in his right arm (140/88 mmHg) compared with his left arm (127/80 mmHg). Initial electrocardiography (ECG) findings are shown in Fig. 1A. Plain chest roentgenography showed neither cardiomegaly nor pulmonary congestion, and trans-thoracic echocardiography showed no evidence of a wall motion abnormality of the left ventricle, significant valvular dysfunction, pericardial effusion, or left ventricular hypertrophy. Initial blood analysis showed abnormally elevated creatine kinase (CK) (283 IU/l), CK-MB (41 IU/l), and troponin I (6.45 ng/ml) levels. Emergency contrast-enhanced computed tomography (CT) showed no evidence of aortic dissection. Subsequently, however, he complained of chest oppression concomitant with back pain, palpitations, and heavy sweating. A second ECG showed T inversion in the V4–6 leads (Fig. 1B). His blood pressure rose to 240/120 mmHg. Within 5 min after sublingual nitrate spray, his symptoms vanished completely, and his blood pressure normalized (130/70 mmHg). Because of a preliminary diagnosis of probable acute coronary syndrome, we performed

emergency coronary angiography, which showed a coronary artery aneurysm, measuring 15 mm × 6 mm, in the distal portion of his left anterior descending artery, along with coronary flow delay (thrombolysis in myocardial infarction grade 2) caused by stasis of blood flow at the coronary aneurysm (Fig. 2A and B). No significant coronary stenosis was found at either the inflow or the outflow tract of the coronary artery aneurysm. No notable findings were observed in the right coronary artery. During coronary angiography, his blood pressure also rose periodically concomitant with the same symptoms and ECG changes. His condition stabilized in the intensive care unit with treatment with low-dose aspirin, intravenous unfractionated heparin, and intravenous diltiazem.

Re-analysis of the blood sample taken in the Emergency Service department showed that the patient's plasma catecholamine concentrations were elevated (epinephrine, 2577 pg/ml; norepinephrine, 923 pg/ml; dopamine, 49 pg/ml). Glucagon test was performed while monitoring blood pressure. Following injection of 1 mg glucagon, the patient's blood pressure rose from 120/70 mmHg to 140/90 mmHg, and his plasma catecholamine concentrations were significantly elevated. A 24-h urine specimen also showed a large quantity of secreted catecholamine metabolites (Table 1). Re-evaluation of the previous CT images revealed that the right adrenal tumor had increased in size, from 26 mm × 20 mm to 29 mm × 21 mm over 7 months (Fig. 3A and B). ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy revealed positive radioactive uptake by this tumor, but distant metastases were not observed (data not shown). Paroxysmal pheochromocytoma concurrent with coronary artery aneurysm was finally diagnosed. The patient's symptoms subsequently stabilized with doxazosin (4 mg/day), low-dose aspirin (100 mg/day), and sustained-release diltiazem (200 mg/day).

Approximately 1 month later, the patient underwent laparoscopic excision of the right adrenal tumor. He recovered uneventfully following surgery. Histologic examination of the specimen showed tumor cells in the adrenal gland containing both amphophilic granule-containing cytoplasm and a clear nucleus proliferating in a nodular pattern, and compressing the normal

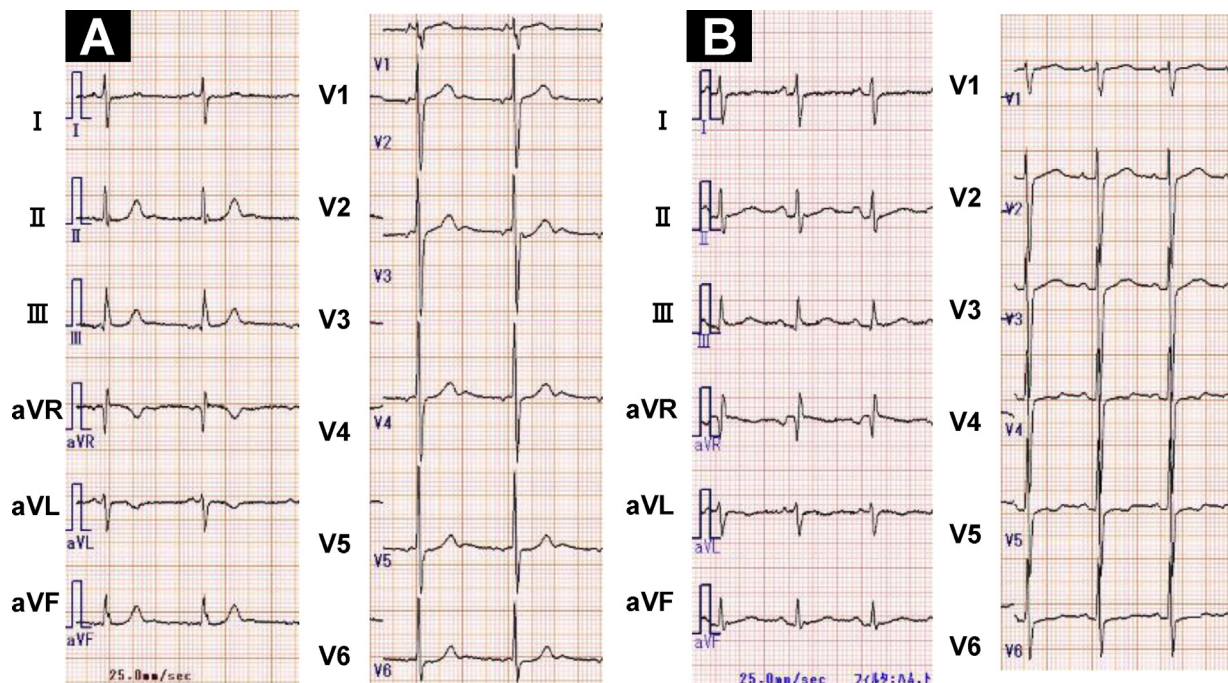


Fig. 1. (A) Initial electrocardiography (ECG) showed no remarkable findings except for ectopic atrial rhythm. (B) The second ECG when he complained of chest symptom soon after contrast-enhanced computed tomography showed T inversion in the V4–6 leads.

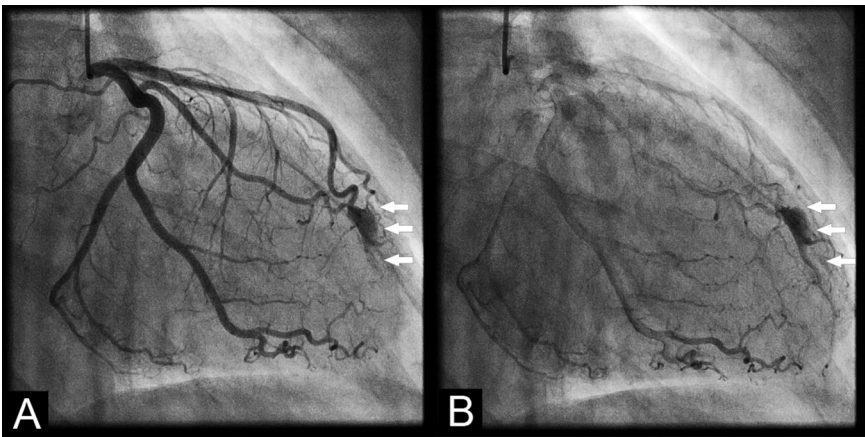


Fig. 2. Coronary angiography (A, early phase; B, late phase) showed a coronary artery aneurysm, measuring 15 mm × 6 mm, in the distal portion of his left anterior descending artery concomitant with coronary flow delay (arrow).

Table 1
Endocrinological tests.

	Initial examination	Stored blood sample (ES)	Second examination	Glucagon test	Normal range
<i>Plasma</i>					
Epinephrine	65	2577	359	264 → 473	<100 pg/ml
Norepinephrine	174	923	408	386 → 484	100–450 pg/ml
Dopamine	9	49	7	<5 → 6	<20 pg/ml
<i>Urinary</i>					
Epinephrine	31.5	ND	885.6	ND	3.4–26.9 µg/day
Norepinephrine	128.0	ND	501.3	ND	48.6–168.4 µg/day
Dopamine	664.0	ND	639.0	ND	365.0–961.5 µg/day
Metanephrine	1.54	ND	4.63	ND	0.04–0.18 mg/day
Normetanephrine	0.36	ND	0.93	ND	0.10–0.28 mg/day

ND, not determined; ES, Emergency Service department.

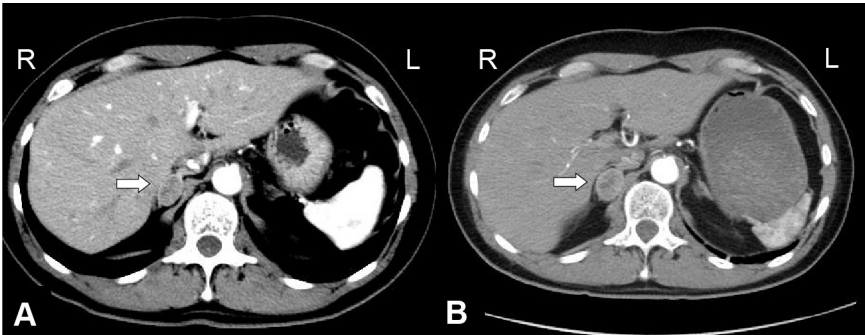


Fig. 3. Contrast-enhanced computed tomography images revealed that the right adrenal tumor had increased in size, from 26 mm × 20 mm (A) to 29 mm × 21 mm (B) over 7 months.

adrenal cortex (Fig. 4A and B). These findings are consistent with a preoperative diagnosis of pheochromocytoma.

The patient was discharged on the eighth post-operative day. He was normotensive, and his symptoms had completely resolved. A year after the surgical excision of the adrenal pheochromocytoma, follow-up contrast-enhanced CT confirmed no recurrence of the pheochromocytoma, and he underwent a treadmill exercise test. ECG at the peak exercise revealed ST depression in the II, III, aVF, and V4–6 leads (Fig. 5).

Discussion

Although pheochromocytomas are relatively rare tumors, they are relatively highly prevalent (up to 0.05%) in autopsy studies, suggesting that many tumors are missed and can cause sudden death or premature mortality [3]. Sporadic forms of pheochromocytomas

are the most common (90%) and are usually diagnosed in individuals aged 40–50 years. However, hereditary forms can also occur in association with familial syndromes (e.g. Von Hippel–Lindau syndrome, multiple endocrine neoplasia type 2, and neurofibromatosis type 1); these are usually diagnosed before the age of 40 years [4]. Our patient likely had the sporadic form because of a lack of family history and his clinical characteristics.

Patients with pheochromocytoma may present with headaches, palpitations, sweats, pallor, and sustained or paroxysmal hypertension due to excess catecholamine secretion. Our patient showed an atypical presentation, with chest oppression concomitant with back pain and mild obesity.

Generally, contrast-enhanced CT is considered a contraindication in patients with pheochromocytomas, because the contrast medium can induce the tumor cells to secrete catecholamines [5]. In our patient, the rapid increase in blood pressure after

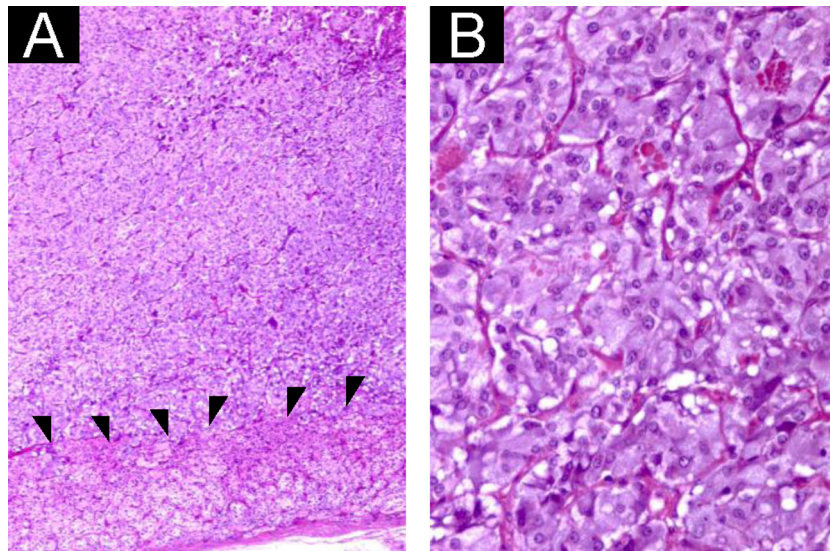


Fig. 4. (A) A tumor of the adrenal medulla proliferates in a nodular pattern, compressing adjacent adrenal cortex (arrow). (B) The tumor is composed of cells containing both amphophilic granule-containing cytoplasm and a clear nucleus.

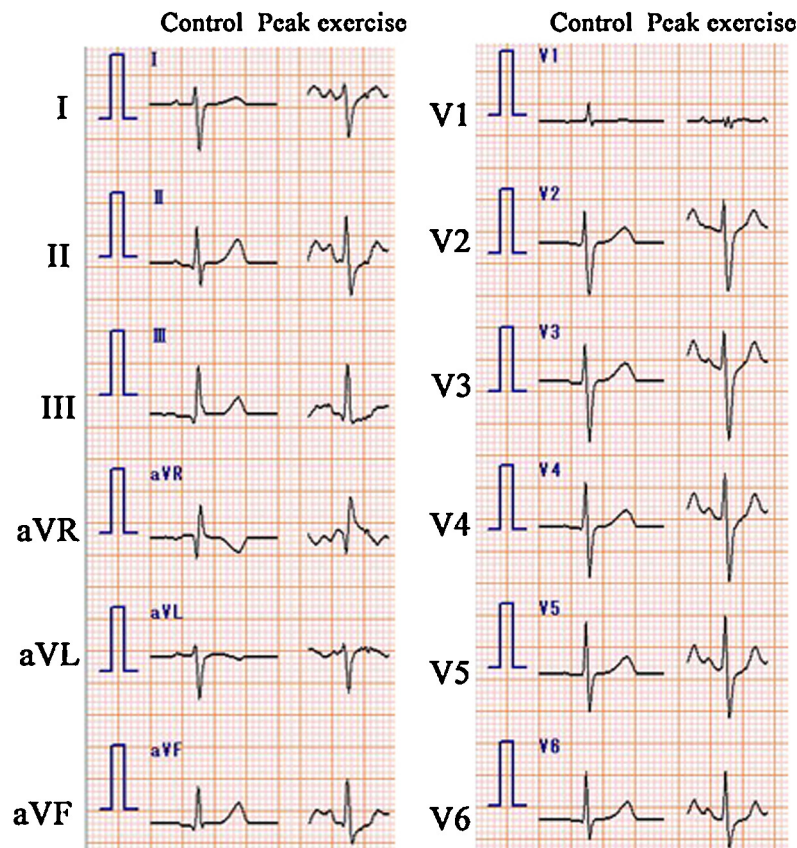


Figure 5. Treadmill exercise test after the surgical excision of the adrenal pheochromocytoma. Electrocardiograph at the peak exercise showed ST depression in the II, III, aVF, and V4–6 leads.

contrast-enhanced CT and re-analysis of the stored blood sample resulted in an accurate diagnosis. The incidence of adrenal incidentaloma has been increasing with advances in imaging modalities [6]. Mantero et al. conducted a study of 1096 cases over 15 years and reported that the most adrenal incidentalomas are non-functional adenoma (74.0%). Functional tumors rank second with an incidence of 14.8% (cortisol-secreting adenoma, 9.2%; aldosterone-secreting adenoma, 1.4%; pheochromocytoma, 4.0%),

followed by other adrenal masses (6.4%), primary adrenal carcinomas (4.0%), and metastases (<1%) [7]. Monitoring blood pressure and/or an analyzing stored blood samples are needed to identify pheochromocytomas in patients with adrenal incidentalomas who undergo contrast-enhanced CT or treatment with glucagon. It should be noted that pre-treatment with an α -blocker is necessary when patients who are likely to have pheochromocytoma need to undergo contrast-enhanced CT.

The serious and potentially lethal cardiovascular complications of these tumors are attributable to the potent effects of secreted catecholamines. Patients with pheochromocytomas may present with acute heart failure and acute pulmonary edema, despite having normal coronary arteries [8], and may display acute ECG changes mimicking acute coronary syndrome [9,10], malignant cardiac arrhythmia, and aortic dissection [1]. Our patient presented with chest oppression concomitant with back pain, a relatively atypical symptom in patients with pheochromocytoma, accompanied by elevated blood pressure and cardiac enzyme concentrations and ischemic ECG changes. Emergency coronary angiography showed a coronary artery aneurysm concomitant with coronary flow delay. This coronary artery aneurysm itself, however, could not explain the extent of myocardial injury because (a) preoperative adenosine-stress myocardial perfusion imaging could not detect the myocardial ischemia or infarction (data not shown) and (b) patterns of ECG leads in which ST-T changes were observed at the treadmill exercise test after the surgical excision of the adrenal pheochromocytoma (Fig. 5) differed from those of the ECG when the patient complained of chest symptoms after contrast-enhanced CT and when he underwent coronary angiography before surgery. We concluded that myocardial injury in our patient might have been caused by relative myocardial ischemia and/or multi-vessel coronary artery vasospasm at the time when excess catecholamines were secreted from the pheochromocytoma rather than by the ischemia that occurred specifically in the area of the coronary artery aneurysm.

When assessed in the emergency room, alternatively measured blood pressure showed differences between the right and left arms in our patient, but simultaneously measured blood pressure showed no significant difference under stable conditions following admission, a finding suggestive of the effect of trace concentrations of paroxysmally secreted catecholamines.

Coronary artery aneurysms are often encountered in clinical cardiology practice, with an incidence of 1.4% in autopsy cases [11] and 4.9% in patients with suspected coronary artery disease who undergo coronary angiography [12]. Coronary artery aneurysms are commonly associated with atherosclerosis and with inflammatory, infectious, and iatrogenic diseases and are often located in the proximal coronary artery [2]. Although their natural history is unclear, the prognosis of most patients is better than that of patients with coexistent obstructive coronary artery disease [2]. The management of coronary artery aneurysms depends on their underlying etiology, the presence and degree of coexisting obstructive coronary artery disease, associated symptoms, and any complications of the coronary artery aneurysm itself (e.g. compression of adjacent structures, fistula formation, and thrombosis with distal embolism) [2]. In these situations, patients are often treated surgically. Our patient had few coronary risk factors, with coronary angiography showing minimal atherosclerotic lesions. Furthermore, his coronary artery aneurysm was located in the distal portion of the left anterior descending artery, suggesting atypical for an atherosclerotic etiology. We chose to treat the coronary artery aneurysm of our patient with low-dose aspirin (100 mg/day) and sustained-release diltiazem (200 mg/day) before and after laparoscopic adrenalectomy [13].

The relationship between pheochromocytoma and coronary artery aneurysm remains unclear. Several patients with pheochromocytoma complicated with an arterial aneurysm (e.g. in the renal [14,15], adrenal [16], cerebral [17], pancreaticoduodenal [18], or abdominal artery [19]) have been described to date. These cases suggest that arterial aneurysm is rare but can be a complication of pheochromocytoma; however, we could not find any earlier reports

that referred to the etiology (e.g. pathological findings) of arterial aneurysm. In our case, it is also uncertain whether coronary artery aneurysm is the secondary complication of pheochromocytoma or the incidental concurrent disease. However, the coronary artery aneurysm in this case was located in the distal portion of the left anterior descending artery although it is usually located in the proximal coronary artery. Our patient had no history of ischemic heart disease, Kawasaki disease, syphilis, or systemic vasculitis, all of which may result in development of a coronary artery aneurysm. These findings support the hypothesis that the coronary artery aneurysm in this case might be a secondary complication of pheochromocytoma.

The incidence of coronary artery aneurysm in patients with pheochromocytoma is difficult to determine because coronary angiography is rarely performed in patients with these tumors. To the best of our knowledge, this is the first report of a patient with pheochromocytoma concurrent with a coronary artery aneurysm.

Conflict of interest

Authors declare no conflict of interest.

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